Replace the paragraph on page 3, line 34 with the following.

A7

The spacer can be any spacer group of dimensions approximately equivalent to an alkyl chain of 1 to 6 carbon atoms, and may for example be a straight or branched alkyl, alkenyl or alkynyl chain of 1 to 6 carbon atoms, which may optionally be susbstituted. The spacer also comprises a cyclic alkyl, alkenyl, or alkynyl group. Preferably the spacer group is unsubstituted, and more preferably is of 2 to 3 carbons atoms. The charged group may be any group which has the ability to restrict access of the compound of formula I to the central nervous system, and is preferably an amidine or guanidine group.

Replace the paragraph on page 33, line 10-14 with the following.

A8

The effects of compounds KRS-3-56 and KRS-41 on the central nervous system were compared with that of morphine using a standard Irwin test (Irwin, S.; Psychopharmacologic (Berlin), 1968 13 222-257). The relevant results are shown in Tables 4 and 5.

In the Claims:

Cancel claims 26 and 27, and amend claims 1, 2, 4-7, and 11-30 as follows.

A9

1. (Amended) A compound of formula I:

(Y-N)-(spacer)-(charged group),

I

where said compound has activity at opiate receptors and wherein Y is an opioid that is structurally related to morphine, N is a nitrogen atom that corresponds to position 17 of morphine, to which is linked a spacer, which links said compound to a charged group or a pharmaceutically acceptable salt thereof.

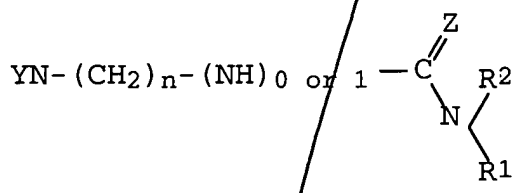
2. (Amended) A compound according to Claim 1, in which the spacer is a straight or branched alkyl, alkenyl or alkynyl chain of 1 to 6 carbon atoms, which may optionally be substituted.

4. (Amended) A compound according to Claim 1, in which the spacer group is unsubstituted.

5. (Amended) A compound according to Claim 1, in which the spacer group is of 2 to 3 carbon atoms.

6. (Amended) A compound according Claim 1, in which the charged group is an amidine or guanidine group.

7. (Amended) A compound according to Claim 1, of formula (II)



in which

YN- represents an organic residue obtained by removal of the R group from an opioid structurally related to morphine of formula (IIIa)

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is O, S or NR^3;

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

R^1 and R^3 may together complete an addition ring, or a pharmaceutically acceptable salt thereof.

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11. (Amended) A compound according to Claim 8, in which n is 2 or 3.

12. (Amended) A compound according to Claim 8, in which Z is NH, and R^1 and R^2 are both H.

13. (Amended) A compound according to Claim 8, in which the opioid structurally related to morphine is a compound selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, etorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine and metazocine.

14. (Amended) A compound according to Claim 12, in which the opioid structurally related to morphine is morphine, codeine or buprenorphine.

15. (Amended) A compound according to Claim 1, in which the opioid structurally related to morphine is selected from the group consisting of morphine, codeine, ethylmorphine, heroin, O-carboxymethylmorphine, O-acetylmorphine, disilyl morphine, disilyl normorphine, etorphine, acetorphine, diprenorphine, buprenorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, metopon, phenomorphan, levorphanol, dihydrocodeine, thebaine, hydrocodeine, pentazocine, eptazocine and metazocine.

16. (Amended) A compound according to Claim 1, in which the compound of formula I is selected from the group consisting of

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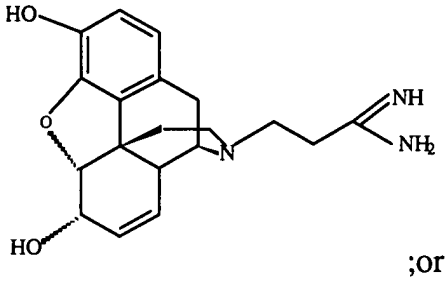

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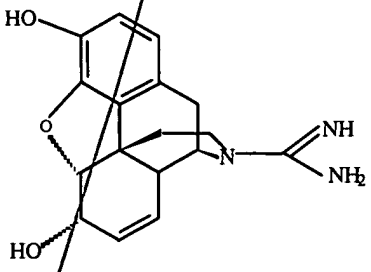

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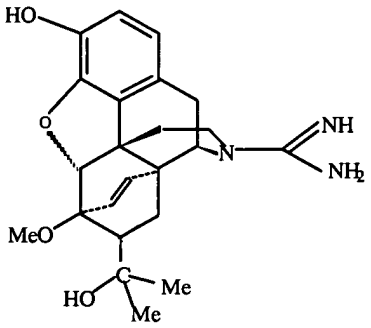

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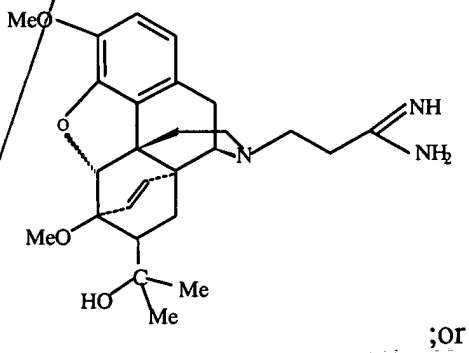

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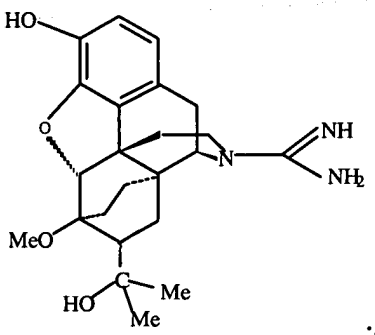

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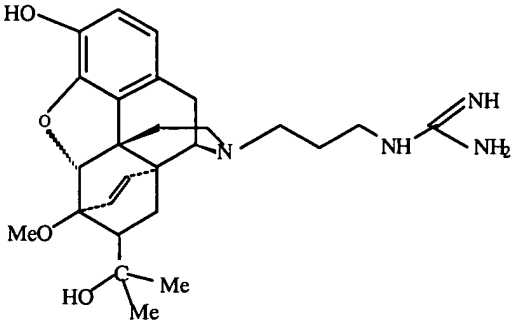

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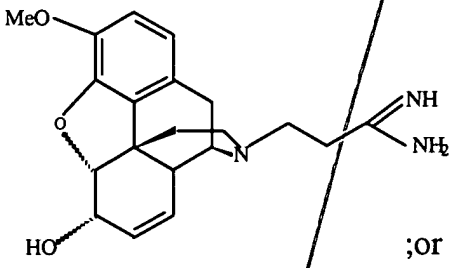

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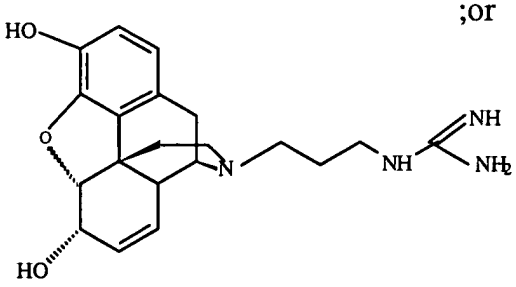

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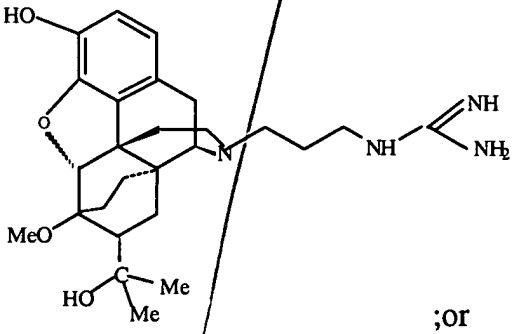

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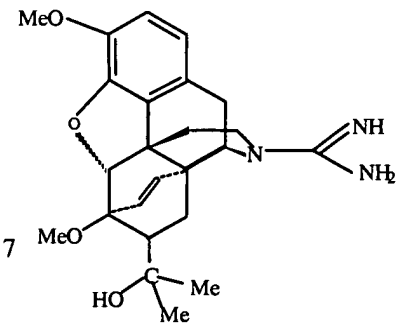


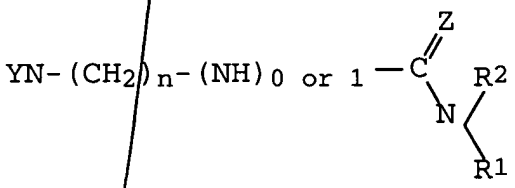
17. (Amended) An opiate receptor agonist having analgesic properties and having reduced or no CNS activity, of formula I:

(Y-N)-(spacer)-(charged group),

I

Where said compound has activity at opiate receptors and wherein Y is an opioid that is structurally related to morphine, N is a nitrogen atom that corresponds to position 17 of morphine, to which is linked a spacer, which links said compound to a charged group or a pharmaceutically acceptable salt thereof,

or general formula II:



(II)

in which

YN- represents an organic residue obtained by removal of the R group from an opioid structurally related to morphine of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is O, S or NR^3;

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

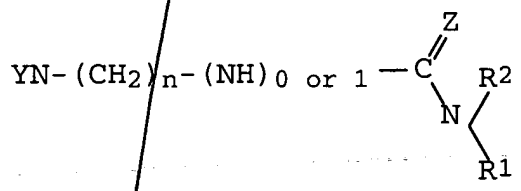
n is an integer of 1 to 6,

and wherein

R^1 and R^3 may together complete an addition ring.

18. (Amended) A method of reducing the central nervous system activity of an opioid structurally related to morphine, comprising the step of linking the nitrogen atom at position 17 of said opioid structurally related to morphine to a spacer group, which in turn is linked to a charged group.

19. (Amended) A method for the preparation of a compound of formula II



in which

YN- represents an organic residue obtained by removal of the R group from an opioid structurally related to morphine of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is O, S or NR^3;

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

R^1 and R^3 may together complete an addition ring,

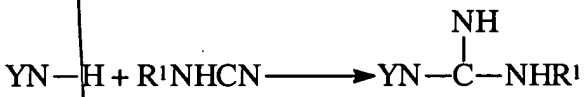
comprising the steps of

(a) Reaction of a compound of formula (IV)

YN-H

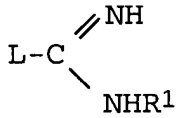
(IV)

with a cyanamide, R^1NHCN, according to the equation



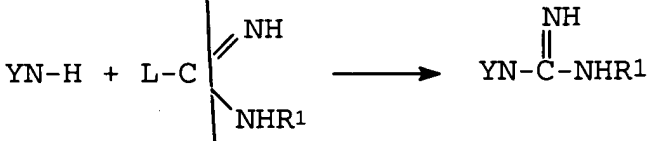
or

(b) Reaction of a compound of formula (IV) with a compound of formula (V)

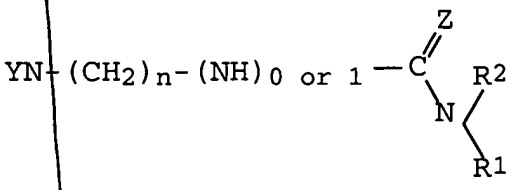


(V)

wherein L is a leaving group, according to the equation



20. (Amended) A method for the preparation of a compound of formula II



in which

YN- represents an organic residue obtained by removal of the R group from an opioid structurally related to morphine of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is O, S or NR^3;

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

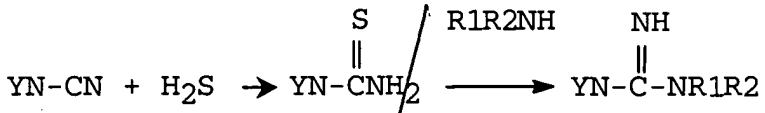
R^1 and R^3 may together complete an addition ring, comprising the steps of

(a) Reaction of a compound of formula (VI)

YN-CN

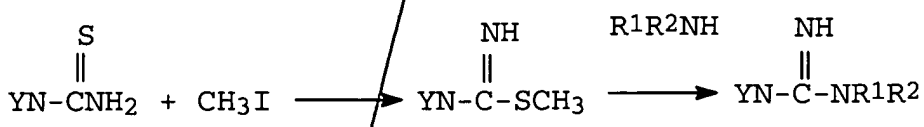
(VI)

with H_2S to obtain an N-thiocarboxamide YN-$CSNH_2$, and optionally reacting the YN-$CSNH_2$ with an amine R^1R^2NH according to the first stage or optionally the two stages of the equation

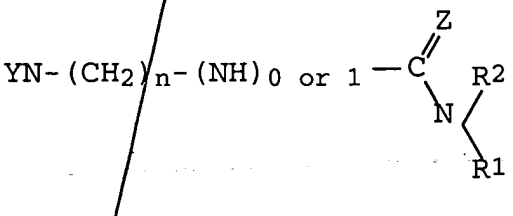


to yield a compound of formula II where Z is S if the optional step is not taken, or a compound of formula II where Z is NH if the optional step is taken, or

(b)



21. (Amended) A method of synthesis of a compounds of formula (II)



(II)

in which

YN- represents an organic residue obtained by removal of the R group from an opioid structurally related to morphine of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is O, S or NR^3;

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

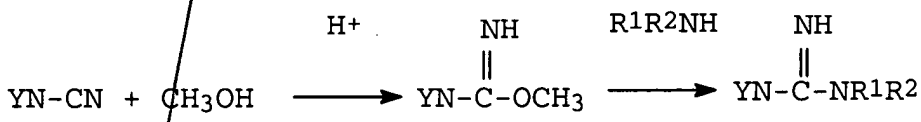
and wherein

R^1 and R^3 may together complete an addition ring,

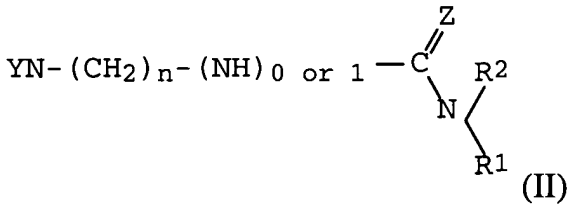
comprising the step of reacting an N-cyano compound of formula (VI)

YN-CN

with methanol under acidic conditions to yield an isourea, which in turn is reacted with an amine according to the equation



22. (Amended) A method of synthesis of a compound of formula (II)



(II)

in which

YN- represents an organic residue obtained by removal of the R group from an opioid structurally related to morphine of formula (IIIa)

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

Z is NH;

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

n is an integer of 1 to 6,

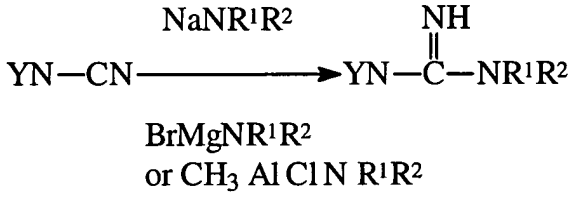
and wherein

R^1 and R^3 may together complete an addition ring,

comprising the step of reacting an N-cyano compound of formula (VI)

YN-CN

and a metallated residue



23. (Amended) A composition comprising a compound according to Claim 1, together with a pharmaceutically acceptable carrier.

24. (Amended) A method of inducing analgesia, comprising the step of administering an effective amount of a compound according to Claim 1 to a mammal in need of such treatment.

A11 Cont'd

25. (Amended) A method according to claim 24, in which the mammal is a human.

Add the following new claims 28-30.

A12

28. (New) A method of inducing analgesia, comprising the step of administering an effective amount of a compound according to claim 7 to a mammal in need of such treatment.

29. (New) A method according to claim 28, in which the mammal is a human.

30. (New) A method of reducing or abolishing the central nervous system activity of an opioid structurally related to morphine, comprising the step of linking said opioid structurally related to morphine via the nitrogen, at position 17 thereof, to a spacer group, which in turn is linked to a charged group.

In the Abstract:

Please add the following abstract to the application on a new page (page 41).

A13

This invention relates to novel structural analogues and derivatives of compounds with general analgesic or related pharmacological activity. In particular the invention relates to derivatives of opioid compounds, particularly morphine and related compounds, in which an opioid compound is linked via the nitrogen at position 17 to a spacer group, which in turn is linked to a charged group, or a pharmaceutically acceptable salt thereof. In particularly preferred embodiments the opioid compound is morphine, codeine, or buprenorphine.